REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The claims have been revised to define the invention with additional clarity. The basis for "(i)" of claim 11 is found in the final paragraph of page 2 of the subject specification. Recitations "(ii)" and "(iii)" find basis in the paragraph spanning pages 3 and 4 of the specification. Support for new claims 18 and 19 can be found in the paragraph bridging pages 3 and 4. That the claims have been revised should not be construed as an indication that Applicant agrees with any position taken by the Examiner. Rather, the revisions are made merely to advance prosecution and Applicant reserves the right to pursue any deleted subject matter in a continuation application.

On page 2 of the Action, the Examiner questions which species of IL-10 is used in the experiment on page 6. The IL-10 utilized was native human IL-10 obtained from Genzyme.

Also on page 2 of the Action, the Examiner objects to claims 1-5 and 7-9. It is submitted that the above-noted claim revisions obviate the Examiner's objections. Reconsideration is requested.

Claims 1-4 stand rejected under 35 USC 101. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions. Reconsideration is requested.

Claims 1-10 stand rejected under 35 USC 112, first paragraph, as allegedly being non-enabled. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions and for the reasons that follow.

The Examiner states at page 4 of the Action that "it is not predictable to one of ordinary skill in the art how to make a functional IL-10 other than ... the full-length IL-10" disclosed."

Applicant submits that both fragments and partially modified forms of IL-10, and methods by which such fragments and forms can be produced, were well known to those skilled in the art at the priority date. An illustrative selection of prior art documents is provided below. As to the question of whether or not such fragments or partially modified forms of IL-10 produced in accordance with these documents would be "functional", it is clearly indicated at page 3 of the specification that, in order to be functional, such an agent must merely retain "the anti-inflammatory healing functionality of IL-10".

The presence or absence of this functionality can be readily assessed using comparative experiments in which the extent of inflammation occurring in wounds treated with the putative agent is compared with inflammation occurring in wounds treated with IL-10. Examples of documents detailing suitable models of wound healing are also provided below.

The Examiner reiterates the factors to be considered in determining whether a disclosure requires "undue experimentation" by the skilled person, as considered in "In re: Wands". The question is to be determined with reference to the following factors:

(1) the quantity of experimentation necessary;

(2) the amount of direction or guidance presented;

(3) the presence or absence of working examples;

(4) the nature of the invention;

(5) the state of the prior art;

(6) the relative skill of those in the art;

(7) the predictability or unpredictability of the art;

(8) the breadth of the claims.

Applicant submits that when these factors are considered it can be seen that there would be no undue burden of experimentation placed upon the skilled person.

1. The quantity of experimentation necessary.

The subject specification clearly discloses the functionality required of a fragment or derivative of IL-10 for it to be suitable for use according to the invention. Applicant notes that published documents available in the art, two examples of which are set out below, disclose well characterized models of wound healing in which the efficacy of such fragments can be readily investigated and compared with the results achieved using IL-10.

Furthermore, it should be noted that the prior art makes available both a number of biologically active fragments and derivatives of IL-10, and also means by which further variants or fragments can be produced. For example, WO 95/03411 discloses a number of derivatives of IL-10 that retain the biological activity of the native molecule, as well as pharmaceutical compositions comprising such fragments and derivatives. WO 95/03411 also discloses methods suitable for the production of further fragments and derivatives capable of use in accordance with the present invention. Indeed, since the sequence of the gene encoding IL-10 was known to those skilled in the art, Applicant submits that the manufacture of further derivatives or fragments based upon IL-10 merely required the use of standard protocols well known to the skilled artisan.

In the light of the extensive teachings in the art, Applicant submits that there would be no undue burden of experimentation on one seeking to put the invention into practice. It would be readily possible for a person of normal skill in the art to consult the available works in order to find details both of biologically active fragments and derivatives of IL-10, and of assays in which these putative agents' activity can be assessed.

For these reasons, Applicant suggests that the degree of experimentation that must be carried out by the skilled person would in no way represent an undue burden.

2. The amount of direction or guidance presented.

The activity required of a fragment or partially modified form of IL-10 suitable for use according to the invention is clearly set out at page 3 of the instant application. This activity, the criterion being that an agent retains "the anti-inflammatory healing functionality of IL-10", is recited in the claims as now presented.

Applicant submits that, since it is the presence or absence of this activity that determines whether or not a fragment or partially modified form of IL-10 is suitable for use in the claimed methods, the identification of this activity as a "benchmark" for assessing therapeutic effectiveness provides adequate direction to the skilled person to enable the identification of suitable agents.

3. The presence or absence of working examples.

The instant specification contains a well-worked example of the use of native human IL-10 to promote healing with reduced scarring. This example thus sets out the activity that must be achieved by an agent in order to be suitable for use according to the invention.

In order to assess whether or not a fragment or modified form of IL-10 is suitable for use according to the invention, the skilled person need only compare the anti-inflammatory functionality achieved by the fragment or modified form with that achieved by native human IL-10 in the example. Such a comparison can be conducted in

accordance with the experimental protocols set out in the present application, or alternatively, in accordance with the assays described in the prior art cited below.

4. The nature of the invention.

The invention, relating as it does to methods suitable for promoting healing with reduced scarring, lies in a field of the art in which a certain degree of experimentation (such as pilot studies, clinical trials etc.), is necessary, for example, in order to meet statutory regulations. This requirement for a certain inevitable degree of experimentation should be considered when assessing what constitutes an undue burden of experimentation on the skilled person.

5. The state of the prior art.

At the priority date of the instant application, a number of fragments and partially modified forms of IL-10, and pharmaceutical compositions comprising same, were known to those skilled in the art. Furthermore, since both the amino acid sequence of IL-10 protein and the DNA sequence of the gene encoding the protein were known to the skilled person, along with a number of suitable techniques for modification of proteins and genes, there existed the potential for further modified forms of IL-10 to be readily generated.

There also existed a wealth of well-validated *in vitro* and *in vivo* human and animal models of wound healing in which the anti-inflammatory properties of such biologically active fragments and modified forms of IL-10 could be investigated.

The selection from the relevant art provided below clearly illustrates that, at the priority date of the instant application, the prior art made available to the skilled person both a wealth of substances representing potentially suitable agents for use according to the invention, the potential to generate further alternative potential agents, and many models by which the suitability of such putative agents could be assessed.

6. The relative skill of those in the art.

Those involved in research leading to the production of novel clinical therapies are familiar with the need to undertake literature searches to identify up to date information regarding the field in question. As such it should be expected that those in this field of art would have been aware of, and have had ready access to, prior art including, and in excess of, that outlined below at the priority date of the instant application.

7. The predictability or unpredictability of the art.

The prior art available to the skilled person provided both examples of fragments and partially modified forms of IL-10, and also a range of methods by which further fragments and partially modified forms of IL-10 could be produced. Thus the art can be regarded as predictable in terms of the ability to produce suitable candidates for use in

accordance with the methods of the invention. Furthermore, the prior art contains many examples of well characterized wound healing models by which the functionality of such candidate agents can predictably be assessed.

8. The breadth of the claims.

Given the ease with which one skilled in the art would be able to identify and produce fragments and partially modified forms of IL-10, and also the ready availability of validated wound healing models by which the suitability of such agents for use in methods of the invention can be ascertained, Applicant submits that the breadth of the presently presented claims is appropriate.

Illustrative examples from the prior art are as follows:

i) Prior art relating to identification and production of biologically active IL-10 fragments and modified forms:

WO 95/03411 (Schering Corporation);

ii) Prior art disclosing suitable wound healing models:

Shah M., Foreman D.M. and Ferguson, M.W.J.
"Neutralising antibody to TGFβ1,2, reduces scarring in adult rodents".
Journal of Cell Science, 107, 1137-1157, 1994

Shah M., Foreman D.M. and Ferguson, M.W.J.
"Neutralisation of TGFβ1 and TGFβ2 or exogenous addition of TGFβ3 to cutaneous rat wounds reduces scarring".
Journal of Cell Science, 108, 985-1002, 1995.

In view of the above, reconsideration is requested.

Claims 1 to 10 stand rejected under 35 USC 112, first paragraph, as allegedly lacking written description. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim amendments and for the reasons that follow.

The claims as now presented now define suitable fragments of IL-10 for use in the methods of the invention with reference to the biological function that must be achieved by such fragments ("a fragment of human IL-10 which retains the anti-inflammatory healing functionality of IL-10"). Applicant believes that this amendment overcomes the Examiner's objection in respect of fragments of IL-10 since such agents are now clearly defined with respect to the anti-inflammatory healing functionality of IL-10. The matter of whether a fragment of IL-10 retains such functionality can be readily assessed by the skilled person using any one of a wide number of published wound healing models.

Furthermore, suitable modified forms, or fragments thereof, for use in the methods of the invention are now defined in terms of both their biological function and their homology with human IL-10 ("a partially modified form of human IL-10, or a fragment thereof, which has at least 60% homology with IL-10 and retains the anti-inflammatory healing functionality of IL-10").

Applicant believes that the definition adopted with respect to partially modified forms of human IL-10 also overcomes the Examiner's rejection. In this instance, the partially modified form, or a fragment thereof, is specified with respect to the anti-inflammatory healing functionality of IL-10 (which can be readily assessed as discussed

above), and also with respect to its homology with IL-10. The degree of homology between modified forms of human IL-10 and native human IL-10 can be readily determined using widely available commercial software packages.

It is submitted that the agents encompassed of the present claims represent members of a genus with a clear and defined function. Reconsideration is therefore requested.

Claims 1-5, 7 and 9 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions. Reconsideration is requested.

Claims 1-10 stand rejected as allegedly representing obviousness-type double patenting over claims 1-10 of USP 6,387,364. It is noted that the rejection can be overcome by the filing of a Terminal Disclaimer and the Examiner is urged to hold the rejection in abeyance until the case is otherwise in condition for allowance.

Claims 1-3, 5, 6, 9 and 10 stand rejected under 35 USC 102(a) as allegedly being anticipated by Gordon et al (WO 93/19770), which discloses the use of IL-4 or IL-10 for the treatment of inflammation (the Examiner is requested to indicate if 35 USC 102(b) was intended). The rejection is traversed.

The present claims relate to the use of the recited agents in promoting healing of wounds or fibrotic disorders with reduced scarring. There is no indication in Gordon et al. that IL-10 can be used to reduce scarring. Applicant, therefore, submits that the claims as now presented are drawn to subject matter not taught by Gordon et al.

Reconsideration is requested.

Claims 1-3, 5, 6, 9 and 10 stand rejected under 35 USC 102(b) as anticipated by Ferguson et al (WO 93/19769), which teaches that growth factors including TNF, PDGF, TGFβ-1, TGFβ-2 and TGFβ-3 can be used to promote healing with reduced scarring. The rejection is traversed.

None of the growth factors recited in Ferguson et al represent agents as defined in the present claims. Specifically, Ferguson et al does not disclose the use of IL-10 or a fragment thereof, and does not disclose the use of a partially modified form of IL-10 having at least 60% homology with human IL-10. Accordingly, the Examiner is requested to reconsider and withdrawn the rejection.

Claims 1-3, 5, 6, 9 and 10 stand rejected under 35 USC 102(b) as anticipated by Schwartz et al (WO 92/11861), which relates to the use of IL-4 in combination with a pharmaceutical carrier. The rejection is traversed.

Applicant submits that IL-4 does not represent an agent falling within the definition set out in the claims as not presented. IL-4 is neither IL-10, nor a fragment thereof. Furthermore, as the Examiner notes, though IL-4 and IL-10 may share greater than 50% homology they do not share at least the 60% homology required of a partially modified form of IL-10 suitable for use according to the invention.

Reconsideration is requested.

Claims 1-3, 5, 6, 9 and 10 stand rejected under 35 USC 102(b) as allegedly being anticipated by Ferguson et al (U.S. Patent 5,972,335). This patent issued October 26,

1999 and thus is not citable under 35 USC 102(b). Indeed, given the priority date of the present application, this patent would not appear to be citable against the present case under any section of 35 USC 102. Clarification of the basis for the rejection is therefore requested.

Claims 1-3, 5, 6, 9 and 10 stand rejected under 35 USC 102(b) as anticipated by Strom et al (U.S. Patent 6,403,077), which discloses the use of pharmaceutical compositions comprising IL-10. The rejection is traversed and the Examiner is requested to indicate if 35 USC 102(e) was intended.

Strom et al provides no teaching relating to the use of IL-10 in the promotion of healing with reduced scarring and thus does not anticipate the instant claims.

Reconsideration is requested.

Claims 4 and 10 and 7 and 8 stand rejected under 35 USC 103 as obvious over Gordon et al, Ferguson et al (WO 93/19769) or Schwartz et al. Withdrawal of the rejections is submitted to be in order in view of the above-noted claim amendments and comments that follow.

None of these documents would have suggested that IL-10, its fragments, or partially modified forms thereof had utility in promoting healing with reduced scarring. Since claim 11 defines non-obvious subject matter, so the claims dependent thereon must also define non-obvious subject matter. The Examiner is therefore requested to reconsider and withdraw the rejections.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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